PA[redacted]NT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

R[redacted] 13 DEC 2004

WIPO PCT

pplicant's or agent's file reference 2396690/EJH	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
ıternational application No. 'CT/AU2004/000043	International filing date *(day/month/year)* 13 January 2004	Priority date *(day/month/year)* 13 January 2003

ıternational Patent Classification (IPC) or national classification and IPC

nt. Cl.[7] C07K 14/47, C07K 14/475, A61K 38/18, A61K 48/00, A61P 3/04, A61P 3/06, A61P 5/04, C07H 21/02, C07H 21/04

ıpplicant

AUTOGEN RESEARCH PTY LTD et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand 15 July 2004	Date of completion of the report 6 December 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **DAVID GRIFFITHS** Telephone No. (02) 6283 2628

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000043

Box No. I Basis of the report

With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1 (b))
- ☐ publication of the international application (under Rule 12.4)
- ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages	as originally filed/furnished	
pages*	received by this Authority on	with the letter of
pages*	received by this Authority on	with the letter of

☐ the claims:

pages	as originally filed/furnished	
pages*	as amended (together with any statement) under Article 19	
pages*	received by this Authority on	with the letter of
pages*	received by this Authority on	with the letter of

☐ the drawings:

pages	as originally filed/furnished	
pages*	received by this Authority on	with the letter of
pages*	received by this Authority on	with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000043

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: **1, 22, 23-28 and 30 (all in part)**

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. **1, 22-28 and 30 (all in part)**
are so unclear that no meaningful opinion could be formed *(specify)*:

The scope of "a derivative or homolog" in claim 1 and "a derivative, homolog, analog, chemical equivalent or mimetic" in claim 28 is so unclear that a meaningful search was not possible and these claim have only been searched to the extent that it does not include any of these terms.

Claims 23-28 and 30 are directed to agents that modulate the effect of the described genes or to the use of such agents. The term 'agents" in its broadest scope is not restricted to any particular family of chemicals and so does not enjoy support from the description in its broadest aspect. The claims have only been searched to the extent that the agents are antibodies or similar molecules whose structures can be directly deduced from the present disclosure because they are not searchable across their entire scopes.

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **1, 22-28 and 30 (all in part)**

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. IV Lack of unity of invention

☐ In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

☐ complied with.

☒ not complied with for the following reasons:

The only feature in common between the claimed sequences is that they are differentially expressed in hypothalamus in obese animals compared to lean animals or in fasted animals compared to fed animals or in diabetic animals compared to non-diabetic animals. However, the feature "differential expression in hypothalamus, in fasted animals compared to fed animals" is not novel since there are other known genes with this feature. Thus, no unity of invention is in evidence *a posteriori*.

4. Consequently, this report has been established in respect of the following parts of the international application:

☒ all parts.

☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Statement

Novelty (N)	Claims	YES
	Claims 1 - 31	NO
Inventive step (IS)	Claims	YES
	Claims 1 - 31	NO
Industrial applicability (IA)	Claims 1 - 31	YES
	Claims	NO

Citations and explanations (Rule 70.7)

The claimed invention relates to a nucleic acid sequences, and proteins from them, that are expressed in larger amount in the hypothalamus of obese animals compared to lean animals, or in fed animals compared to fasted ones. The nucleic acids and proteins are useful in the treatment of various conditions including diabetes and obesity.

The following citations are considered in this report:

D1. WO 2002/062994
D2. WO 2001/002560
D3. WO 2000/064931
D4. WO 2002/008275
D5. WO 1999/023217

WO 2002/062994 relates to nucleic acids expressed in the hypothalamus or muscle tissue in obese animals and discloses several sequences with over 40% identity to the present sequences. For example SEQ ID 2 of the citation has 46.8% identity to present sequence 4. (Note: "Identity" throughout this report ignores any nucleotides, in either the citation or the present sequences, where the nucleotide is shown as *n*, signifying that it can be any nucleic acid — if these were to be taken into account the identities reported would be higher in some instances). The claims cannot be considered as novel or inventive in the light of this citation.

WO 2001/002560 relates to nucleic acids that are differentially expressed in liver. The citation teaches that the hypothalamus plays a central role in energy balance, that it produces various proteins that affect food intake and could contribute to the development of obesity and subsequent diabetes. Given the teaching of the citation the person skilled in the art (PSA) would consider the hypothalamus an obvious organ to look for similar nucleic acids and proteins. The present claims therefore lack an inventive step in the light of this citation. SEQ ID No. 5 of the citation has 44.3% identity to present SEQ ID 8.

WO 2000/064931 discloses ligands of the protein from the "beacon" gene, which is differentially expressed in hypothalamus of lean and obese animals. The citation For example SEQ ID 1 has 43% identity to present sequence 3 and SEQ ID 3 has 44% identity to present sequence 3. The claims cannot be considered as novel or inventive in the light of this citation.

WO 2002/008275 relates to genes expressed in obese rat hypothalamus. Again the citation discloses several sequences with over 40% identity to the present sequences; for example, SEQ 3 has 44% identity to present sequence 2, SEQ 15 has 44% identity to present sequence 5 and SEQ 6 has 49% identity to present sequence 5. The claims cannot be considered as novel or inventive in the light of this citation.

Continued on supplemental sheet...

Box No. VI Certain documents cited

Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X WO 2003/033513	24 April 2003	16 October 2002	16 October 2001
P,X WO 2003/018823	6 March 2003	28 August 2002	29 August 2001
P,X WO 2003/016542	27 February 2003	13 August 2002	14 August 2001

These documents relate to genes that are associated with obesity and type-2 diabetes and are differentially expressed in various tissues including the hypothalamus. They each disclose sequences with over 40% identity to the present sequences: *e.g.* sequence 7 of WO 2003/033513 has 46% identity to present SEQ ID 3; sequence 1 of WO 2003/018823 shows 45.8% identity to present SEQ ID 3 and 48% identity to SEQ ID 5. These documents are relevant to the novelty and inventive step of the present claims.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description states the invention relates to a nucleic acid sequence that is expressed in the red gastrocnemius muscle or its equivalent under certain physiological conditions, however the claims relate to a nucleic acid sequence that is expressed in the *hypothalamus*.

The applicants have disclosed a range of partial nucleotide sequences that are differentially expressed in obese animals as opposed to lean animals or fed *vs* fasted animals. Claim 1 encompasses nucleotide sequences with at least 40% identity to the defined sequences, or nucleotide sequences capable of hybridising to the applicants' sequences under low-stringency conditions. Claims to sequences of such low homology are not supported by the description, nor are claims to sequences capable hybridising under low-stringency conditions. Whilst it can be inferred that highly homologous nucleotides will have highly similar functions it cannot be inferred that this will necessarily be so with sequences of lower homology.

The scope of "a derivative, homolog, analog, chemical equivalent or mimetic of said protein" in claim 22 and similar wording in subsequent claims is much broader than could possibly be supported by the description and is so broad as to be almost meaningless.

The scopes of such terms as "a modulator of ..." in claim 23, "a modulating effective amount of a molecule" in claim 24, and "an agent" in claim 25 do not restrict the modulators defined to any particular chemical family. Without a restriction that would limit the agents or modulators to those that would be directly derivable from the present disclosure (*e.g.* antibodies or antisense molecules) claims that include such terms are too broad to be fully supported by the description.

Claim 1 defines the nucleic acid molecules as being expressed in larger amounts in the hypothalamus under certain conditions compared to others. It is not clear however if this differential expression is intended to apply to all claimed sequences: it is not clear that this condition applies to the "derivative or homolog" defined in line 2 or if it applies to the nucleotide sequence capable hybridising (under low-stringency conditions) to the sequences defined in points (i) to (ix). See also claim 11 in this regard.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

WO 1999/023217 relates to nucleic acids that encode the "beacon" proteins that are associated with the modulation of obesity, diabetes and metabolic energy levels. The gene is exemplified from the hypothalamus of *Psammomys obesus*. SEQ 3 of the citation has 44% identity with present sequence 3. The claims cannot be considered as novel or inventive in the light of this citation.

All claims meet the criterion of being industrially applicable.

Note:

- The ANGIS and DGENE searches revealed a large number of sequences with 80% or more identity with the present sequences. However, if there was no indication of differential expression of the sequences under different physiological conditions these sequences were not considered as being citable. However, given the claims include nucleic acids sequences capable hybridising under low-stringency conditions it may be that many of these sequences fall within the scope of the present claims.
- Many of the citations disclose primers with identities in the rage of 50 to 60% identity or higher compared with the present sequences and would have the ability to bind to the present sequences under low-stringency conditions. Although, these primers have not been specifically referred to above they may also fall within the scopes of the claim.